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EFFECT OF EXERCISE AND ENVIRONMENTAL HEAT ON DRUG
KINETICS(U) BEN-GURION UNIV OF THE NEGEV BEERSHEBA
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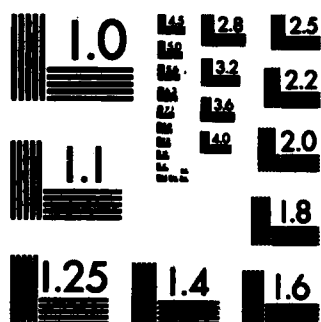
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**EFFECT OF EXERCISE AND
ENVIRONMENTAL HEAT ON
DRUG KINETICS**

**BEN-GURION UNIVERSITY OF THE NEGEV
Research & Development Authority
P.O. Box 653
Beer-Sheva, Israel.**

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PROF. ABRAHAM DANON

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The effects of physical exercise and heat exposure on the pharmacokinetic behavior of some model drugs were investigated in normal volunteers. Drugs were chosen to represent particular kinetic processes. Exercise was mild to moderate and environmental temperature was either 22°C or 40°C. Under heat exposure and exercise, theophylline exhibited prolonged half-life and reduced clearance, suggesting the need for dosage adjustment in moderately active individuals. Exercise influenced digoxin kinetics by		

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shortening the time to peak, probably by enhancing the drug's absorption. The plasma kinetics of quinidine were unchanged under exercise conditions. However, urinary excretion of the drug was significantly higher during exercise than at rest, and this correlated with increased urinary output during exercise. Exercise and heat exposure prolonged the time of distribution of intravenously administered propranolol, while other pharmacokinetic parameters relating to propranolol remained unchanged. The half lives ($T_{1/2}$) of both sulfamethoxazole and trimethoprim that were administered as co-trimoxazole were not significantly altered. The absorption of methylsalicylate that was applied on the skin was markedly influenced by the conditions tested. Thus, the amount of salicylate that was absorbed increased three fold while the subjects were exposed to either heat or exercise or both.

It is concluded that mild to moderate physical activity and/or heat exposure may exert significant influence on the pharmacokinetic behavior of drugs and should therefore be considered as a factor that contributes to interindividual differences in their response to drugs.

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Environmental factors, such as nutrition (1), cigarette smoking (2) or exposure to certain drugs (3) have been shown to produce significant variations in oxidative drug metabolism and other pharmacokinetic processes in man. Less well known are the possible effects of physical exercise and/or heat exposure on drug kinetics in man. The following discussion will review briefly some of the major physiological changes that are expected to occur during exercise and/or excessive environmental heat (4,5), relevant to pharmacokinetic processes that may be influenced.

During exercise, heart rate and cardiac output increase with the intensity of the work load. The regional distribution of blood flow with increasing work load is, however, uneven. Skeletal muscles, which receive some 15-20% of cardiac output during rest (some 1 liter/min), may increase their flow during exercise to over 80% of cardiac output, i.e. to 16 liters/min. Thus, the absorption of drugs from intramuscular, and indirectly from subcutaneous injections, could be expected to increase substantially during exercise. On the other hand, splanchnic blood flow decreases during exercise, and hepatic blood flow may decrease by some 30% in subjects performing severe exercise (6). One may expect, therefore, that the elimination of drugs that are primarily metabolized by the liver be impaired during exercise. Also, the decrease in renal blood flow, along with changes in body water, hematocrit and plasma volume that occur during exercise (7), may adversely affect the renal clearance of drugs that are largely eliminated by the kidneys. This may involve decreased glomerular filtration of drugs or increased reabsorption secondary to decreased urinary flow. Moreover, strenuous exercise may produce significant accumulation of lactic acid in plasma with subsequent aciduria, which may in turn influence the reabsorption of weakly acidic or alkaline drugs in the tubule. Changes in body fluids may also affect the volumes of drug distribution in the various body compartments. Apart from changes in splanchnic blood flow, exercise may alter gastric emptying and intestinal transit time, all of which may reflect on the rate of absorption of drugs from the gastrointestinal tract. Blood flow to the skin increases considerably with the work load up to 50-60% of VO_{2max} (8) as well as during heat exposure, and may serve to enhance percutaneous absorption of drugs applied on the skin.

Unfortunately, many of these potential effects have not been adequately investigated in man. Few published reports indicate that heat exposure and

exercise may exert profound effects on drug kinetics. Swartz et al. reported that such stress conditions altered the volumes of distribution of two test drugs and their rates of renal excretion in normal volunteers (9). The same authors further reported that the disposition of a drug that is rapidly eliminated by the liver, namely indocyanine green, was also significantly affected by physical stress consisting of exercise, hot environment and fluid deprivation. However, the same environmental conditions failed to affect the plasma clearance of antipyrine, which is slowly eliminated by the liver (10). Similar conclusions were drawn by Theilade et al. (11), and by Klotz and Lücke (12) who studied antipyrine and diazepam respectively. Both drugs are slowly eliminated by the liver, and their metabolism was unaltered by exercise.

Even minor physical alterations, such as a change in posture, have been observed to influence the absorption (13,14) or distribution (15) of certain drugs. This effect has been attributed to delayed gastric emptying in the supine position. More obvious effects of exercise are those on drug absorption from intramuscular (16) and subcutaneous sites of injection (17). It is intriguing that the effect of exercise on diabetic patients receiving insulin has been known for more than half a century (18), while recognition of the mechanism of this phenomenon, namely that exercise served to enhance the absorption of injected insulin, was delayed (17).

MATERIALS AND METHODS

General.

The study protocol has been submitted to and approved by the institution's human use review board according to the Helsinki Declaration. Subjects were non-institutionalized consenting adult volunteers, mainly students of the Ben-Gurion University in Beer-Sheva. All subjects were judged to be in good health on the basis of medical history, physical assessment and screening laboratory evaluation. Subjects with a history or physical evidence of significant gastrointestinal, renal, hepatic, hematological or cardiovascular disease were excluded. Informed consent was obtained in writing, after the nature of the study and potential hazards and possible reactions were explained to each prospective volunteer. It was made clear that any subject might withdraw from the program at any time, should he wish to do so.

Subjects refrained from the use of all drugs, including over-the-counter medication, for at least one week prior to any study. The use of xanthine:

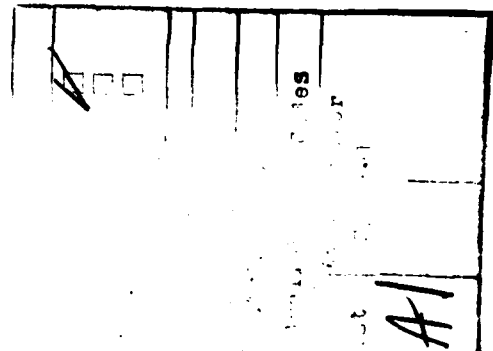
containing beverages such as coffee, tea, chocolate or cola, or alcoholic beverages was prohibited for 12 hours prior to, and throughout the study. Subjects fasted for 12 hours prior to, and 4 hours after dosing. Standard meals were served at 4 hours. All beverages other than water were not permitted during each study period.

Groups of 6 subjects were used for each drug experiment. The drugs were administered under 4 experimental conditions, namely, at rest, with 2 levels of exercise, and exercise in the heat. The order of experiments was randomly assigned. Exercise was accomplished on an ergometric bicycle for periods of 2-6 hours either immediately after drug administration or after the absorptive state was judged to be completed, namely 2-3 h after oral ingestion. Exercise was individualized to 30% (mild) and 50% (moderate) of maximal oxygen uptake ($\text{VO}_{2\text{ max}}$). The latter was determined from the pulse rate, according to Astrand and Ryhming (19). Exercise in the heat (40°C , 20-40% relative humidity) was performed only to 30% of $\text{VO}_{2\text{ max}}$. Control ambient temperature was $22 \pm 2^{\circ}\text{C}$.

Venous blood specimens were obtained by repeated venipuncture, in order to avoid stasis. For each drug, a baseline sample was taken just prior to administration, and then at appropriate intervals according to the pharmacokinetic characteristics of each drug under study. In the percutaneous absorption of methyl salicylate experiments, urine as well as blood was collected, and the output of urinary metabolites, namely salicyluric acid and salicyl glucuronide, were measured as an estimate of the rate and extent of salicylate absorption.

Analytical Methodology

Theophylline concentrations were estimated by spectrophotometry according to Schwetner et al. (20). Digoxin was analysed by radioimmunoassay (21), using ³H-labeled digoxin and antibody made by Miles-Yeda Ltd., Rehovot, Israel. Quinidine was analysed by fluorometry according to Cramer and Isacsson (22). Blood plasma concentrations of propranolol were estimated by HPLC (23). Salicylate in plasma was assayed by fluorometry (24) and urinary metabolites by HPLC (25). The components of co-trimoxazole, namely sulfamethoxazole and trimethoprim, were analysed according to Rieder (26) and Schwartz et al. (27), respectively.



RESULTS

1. Theophylline

The pharmacokinetics of theophylline were studied in 6 healthy volunteers at rest, during light and moderate exercise and during exercise in a hot environment. Exercise was performed between 2 and 4 h after oral ingestion of theophylline in solution at a dose of 200 mg/m² body surface. Significant prolongations of the half-life ($t_{1/2}$) of the drug and reductions in its body clearance were observed during exercise to 30% of $\dot{V}O_{2\text{ max}}$ both at 22 and 40°C, as well as during exercise to 50% of $\dot{V}O_{2\text{ max}}$ at 22°C. $t_{1/2}$ was (mean±SEM) 8.5±0.8, 8.0±1.0 and 7.2±1.0 h at the three exercise sessions, respectively, compared with 6.4±0.9 h at rest. Plasma clearances at the three exercise sessions were 0.70±0.09, 0.62±0.1 and 0.75±0.09 ml/min/kg, respectively, compared with 0.99±0.13 ml/min/kg at rest. The apparent volumes of drug distribution (V_d) decreased significantly at the 50% and the 30% exercise in the heat, suggestive of some dehydration. The areas under the concentration-time curves ($AUC_{0-\infty}$) and the elimination rate constants (K_{el}) also changed significantly under the different experimental conditions. It is suggested that appropriate dose adjustments may have to be made in moderately active patients who are treated with theophylline.

2. Digoxin

Digoxin was taken to represent a drug possessing incomplete oral bioavailability. Thus, its bioavailability has been shown to be influenced by factors that affect gastrointestinal transit time (28).

Digoxin-Teva, that was used in the present study, has an oral availability of some 80%. Two 0.25 mg each of Digoxin-Teva (lot no. 199001) were ingested at 0 time. Then the subjects exercised to 50% of $\dot{V}O_{2\text{ max}}$ for 2 hours or rested at 22°C.

The plasma concentrations of digoxin during the six-hour experiment are shown in Figure 1. The plasma concentration peaked earlier (0.85±0.05 hours) after exercise than at rest (1.46±0.30 hours) - a statistically significant difference ($p<0.05$). Concentrations at 1, 3 and 4 hours also differed significantly between the two sessions. The apparent half-lives - 3.36±0.4 with exercise and 5.80±1.9 hours at rest - were not statistically different. Neither were the areas under the concentration-time curves (5.40±0.73 vs. 6.10±0.65 µg.h/ml).

3. Quinidine

Quinidine is eliminated by both liver metabolism and urinary excretion to varying degrees. It has been shown that the urinary excretion of this drug is influenced by alterations in urinary pH (29). Since strenuous exercise may induce aciduria, it was of interest to study whether this may affect quinidine kinetics.

Two experimental protocols were applied with quinidine. In both, one 200 mg quinidine (Ikapharm Ltd., lot. no. 734028) was ingested initially, then exercise was carried out at either 50% of VO_2 max for 2 hours or 30% of VO_2 max for 4 hours (with 15 min. rest intervals every hour).

The plasma concentrations vs. time curves are shown in Figures 2 and 3. None of the pharmacokinetic parameters that were calculated, namely the peak concentrations or times to peak, the half lives, elimination rate constants and areas under the curves, differed significantly. On the other hand, urinary recovery of the drug was higher during the exercise period (30% of VO_2 max for 4 hours), 9.71 ± 0.74 mg between the 2nd and 6th hour, compared with 6.66 ± 1.12 mg at rest. Although urinary pH remained unaltered, urinary volume increased during exercise (245.6 ± 78.1 , compared with 137.8 ± 28.8 ml between 2-6 hours, $p < 0.05$). This increased output of urine may have accounted for the increased urinary excretion of quinidine. Nonetheless, since urinary excretion is not the sole route of elimination of this drug, plasma parameters were unaffected.

4. Propranolol

Propranolol exhibits a peculiarity known as first pass metabolism (30). It is completely absorbed after oral administration, but is rapidly taken up and metabolised by the liver, even before it reaches the systemic circulation. Therefore, any changes that may occur in hepatic blood flow could influence the extent of this metabolism.

In order to be able to calculate liver blood flow and oral bioavailability of this drug, propranolol was administered to each subject both orally and intravenously, on different occasions. Two 40 mg propranolol tablets (Deralin-Abic) were administered orally. For the intravenous administration 5 mg of propranolol were diluted in 15 ml saline and infused over a period of 20 min. When the drug was administered orally, exercise was performed during the first two hours, i.e. the absorptive phase. In the intravenous study the exercise was done from $\frac{1}{2}$ through $2\frac{1}{2}$ hours.

Plasma concentrations are shown in Figures 4 and 5. In all three exercise sessions the half lives of the distribution phase ($T_{1/2\alpha}$) was significantly larger than in the control experiment ($1.41 \pm 0.22^*$, 1.27 ± 0.31 and $1.43^* \pm 0.13$ hours at 30% of $VO_{2\max}$, 50% $VO_{2\max}$ and 30% $VO_{2\max}$ at 40°C , respectively vs. 0.93 ± 0.17 hours, $p < 0.05$). Likewise, the distribution rate constant was significantly smaller in the exercise sessions ($0.56 \pm 0.09^*$, 0.70 ± 0.14 , $0.54 \pm 0.05^* \text{ h}^{-1}$) vs. the control ($0.84 \pm 0.14 \text{ h}^{-1}$, $p < 0.05$). None of the other parameters that were calculated, namely the peak concentrations and times to peak, the half-lives of the elimination phase, the clearances, volumes of distribution, oral bioavailability and liver blood flow, showed significant differences between exercise and rest.

5. Methyl salicylate (dermal)

This drug was chosen to test the effect of exercise and heat exposure on dermal absorption. Methyl salicylate is usually applied on the skin for its local effects and is thought to be absorbed only to a small degree. After absorption it is hydrolysed and the salicylate is metabolised and excreted in the urine as metabolites. Although salicyluric acid is known as the main urinary metabolite, other metabolites may be present, depending primarily on the dose that is administered. Therefore HPLC was chosen for analysis. The only metabolite identified in measurable quantities was indeed salicyluric acid. The urinary recovery of salicyluric acid during the test period was thus taken as a quantitative measure of the absorption of methyl salicylate.

As can be seen in Figure 6, some 60 mg salicyluric acid appeared in the urine during 8 hours at rest and normal room temperature (out of the 5 g methyl salicylate applied to the skin). However, the rate of absorption increased significantly in all experiments. In exercise at 40°C , the amount of urinary salicyluric acid tripled, indicating markedly enhanced cutaneous absorption.

6. Co-trimoxazole

The constituents of this fixed drug combination, trimethoprim and sulfamethoxazole, are a base ($pK_a=6.4$) and an acid ($pK_a=5.7$), respectively. Both are cleared from the body via the kidneys, the sulfa being partly acetylated. Urinary excretion is not affected significantly by altered renal function, but may be influenced by changes in urinary pH (31).

Our results, presented in Figures 7 and 8, indicate only minor changes in plasma kinetics during heat exposure and exercise. The urinary excretion of the sulfa drug decreased slightly during heat exposure, while that of trimethoprim was augmented under identical conditions, probably reflecting their natures as acid and base, respectively.

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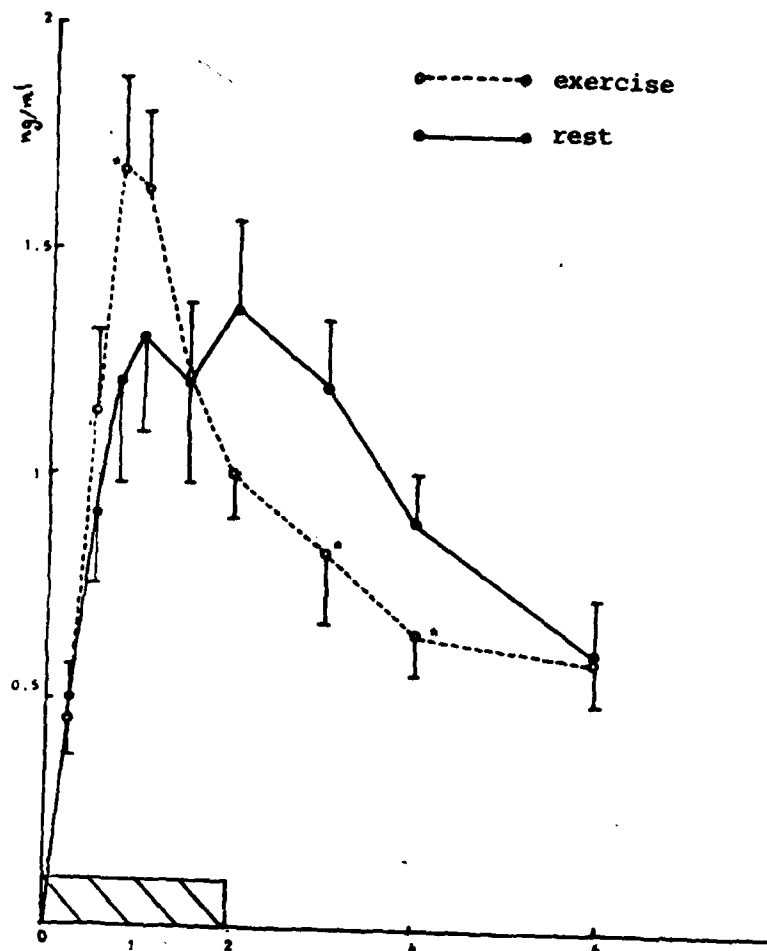


Figure 1: Mean (\pm SEM) plasma digoxin concentration over a 6 hour period after oral ingestion of digoxin. Shaded area represents time of exercise.

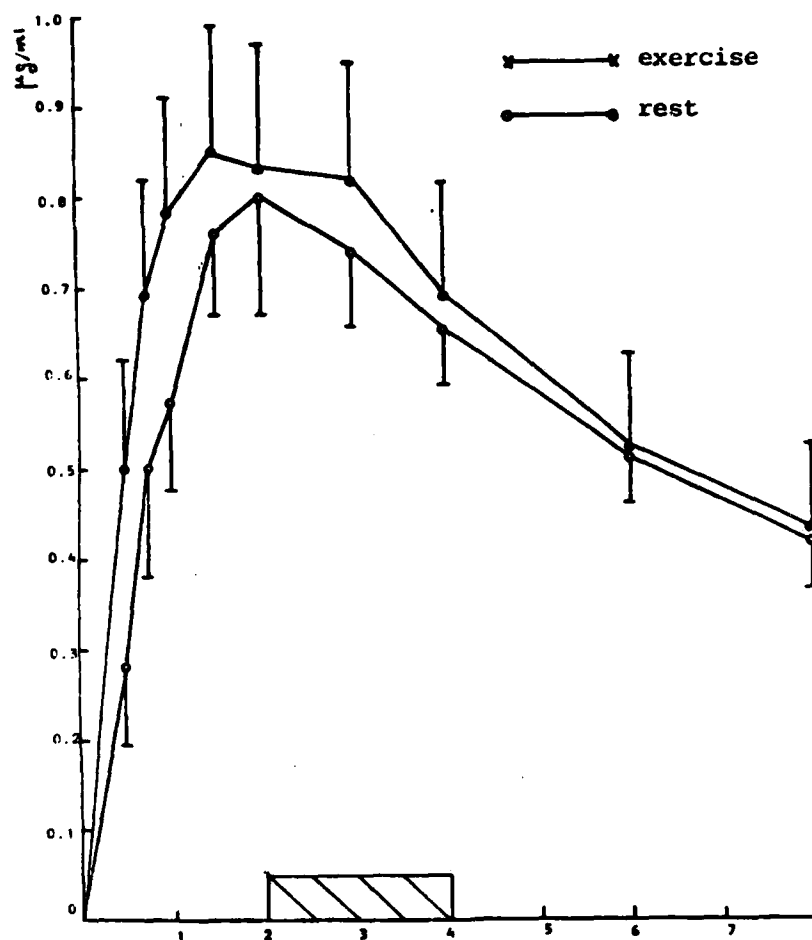


Figure 2: Mean (\pm SEM) plasma quinidine concentrations after oral administration of quinidine. Exercise (or rest, as control) was to 50% of VO_2 max between 2-4 hours.

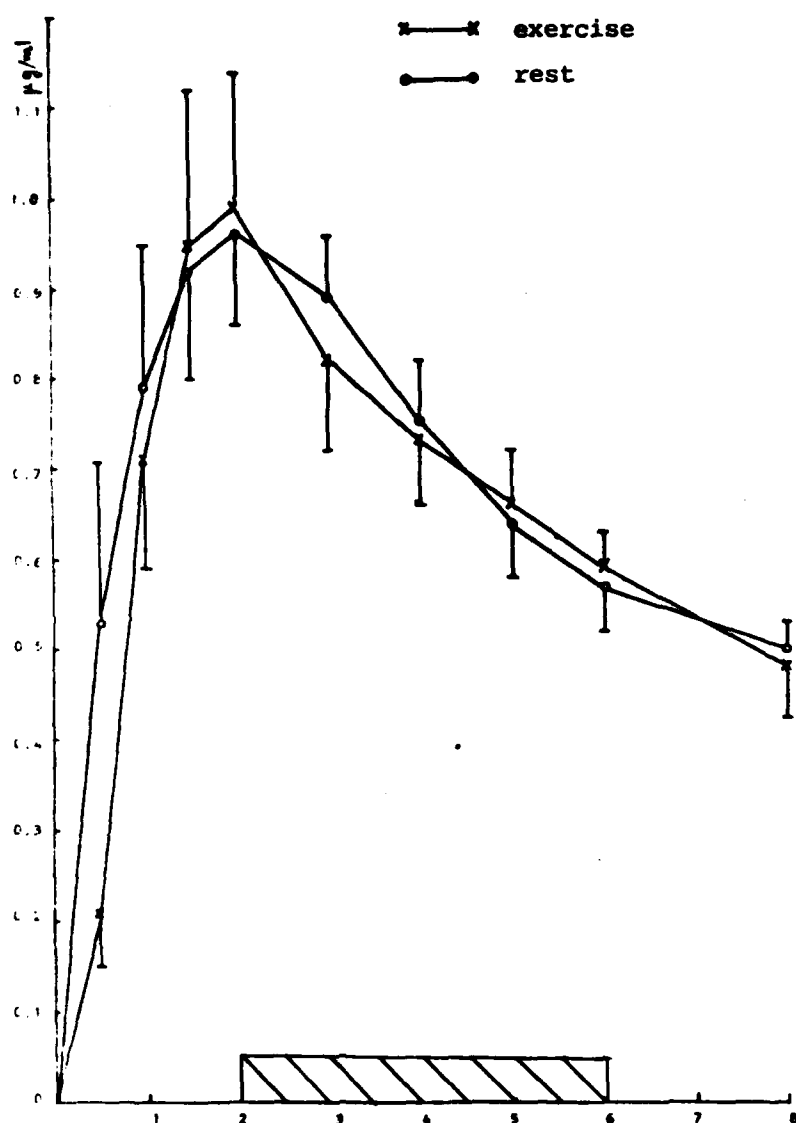


Figure 5: Mean (\pm SEM) plasma quinidine concentrations after exercise to 30% of $VO_{2\text{ max}}$ (shaded area) or at rest.

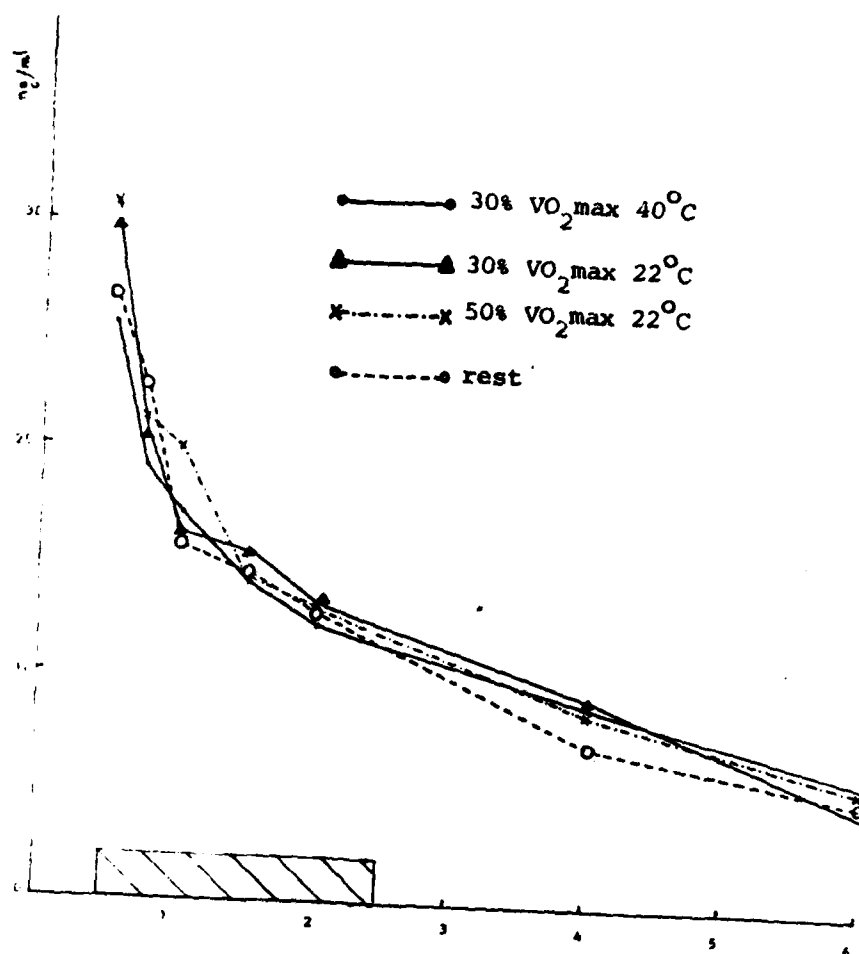


Figure 4: Mean plasma concentrations of propranolol after i.v. administration of 5 mg propranolol. Exercise was performed as indicated by the shaded area.

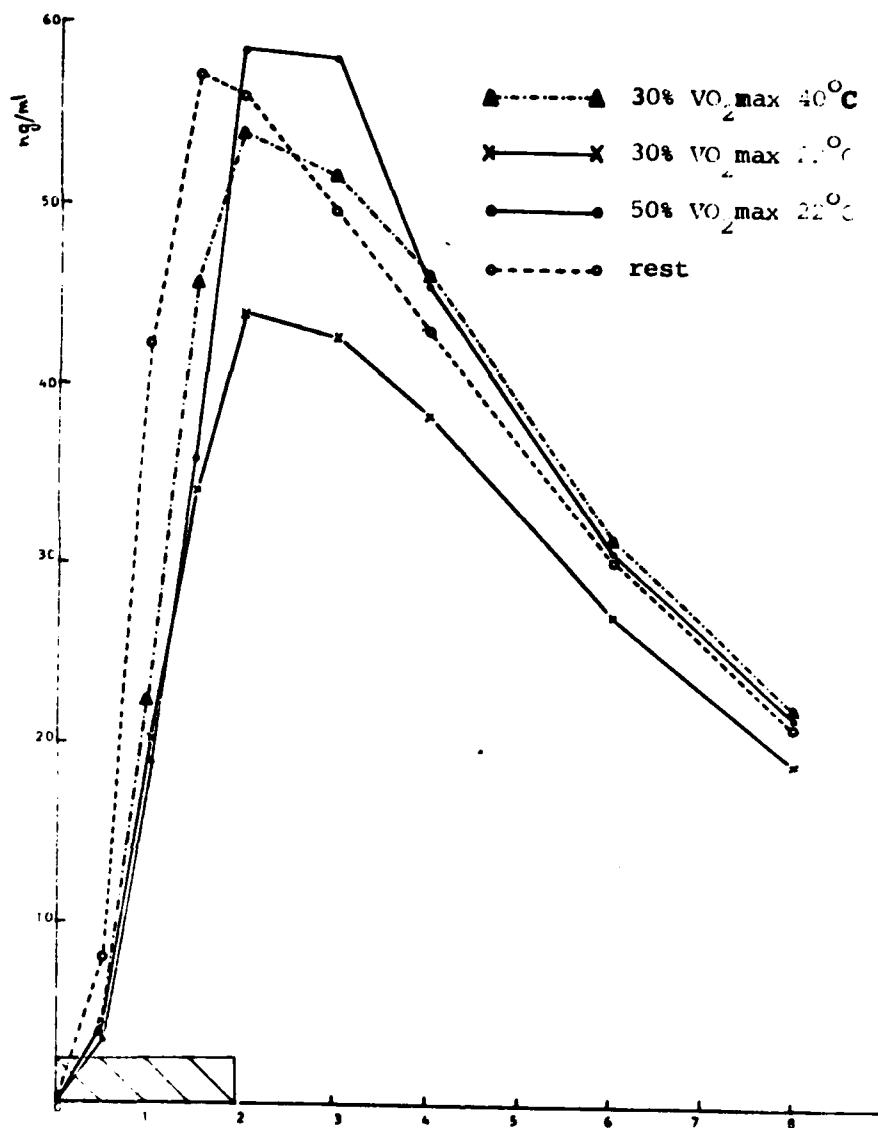


Figure 5: Mean plasma concentrations after oral administration of 80 mg propranolol. Exercise was performed between 0-2 hours.

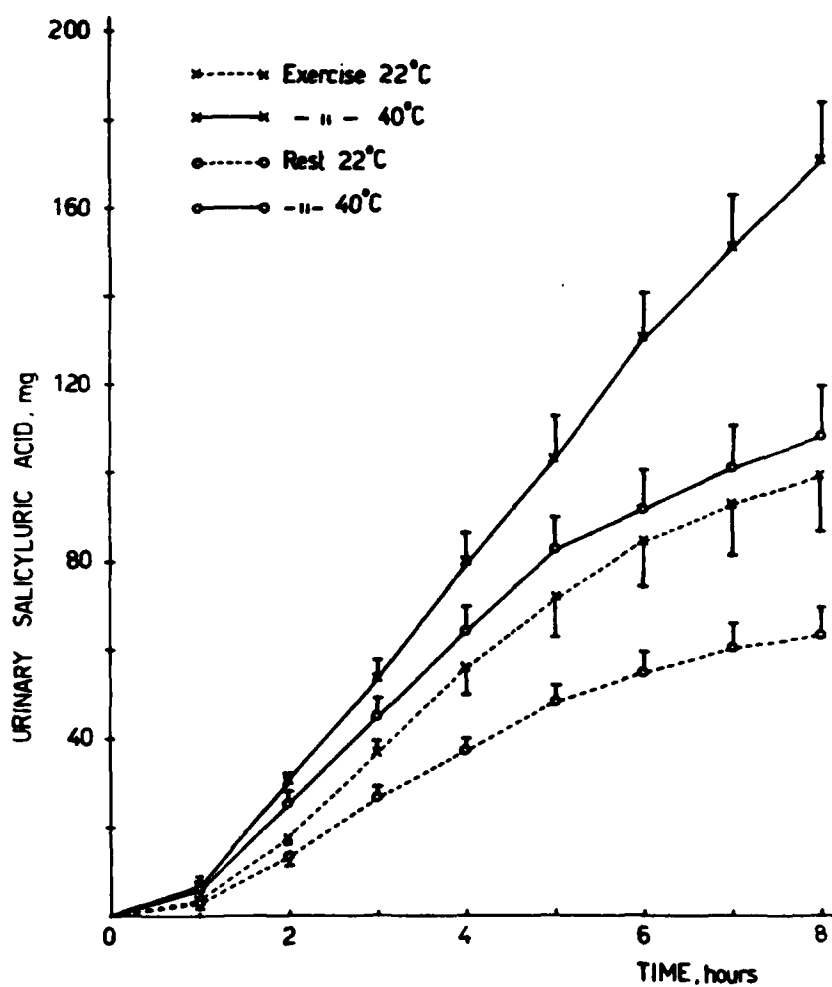


Figure 6: Mean (\pm SEM) urinary output of salicyluric acid after application of methyl salicylate on the skin. Exercise was performed during the first 6 hours.

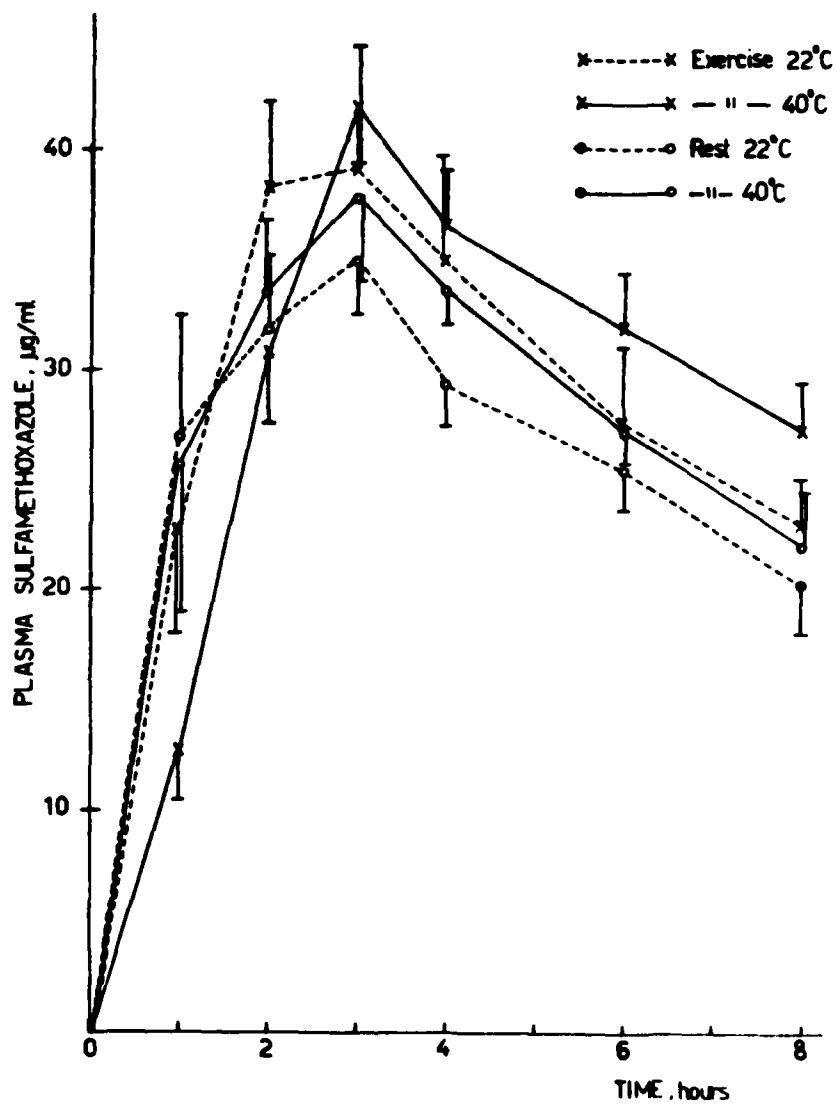


Figure 7: Mean (\pm SEM) of plasma sulfamethoxazole in 6 subjects undergoing exercise and heat exposure, compared with rest.

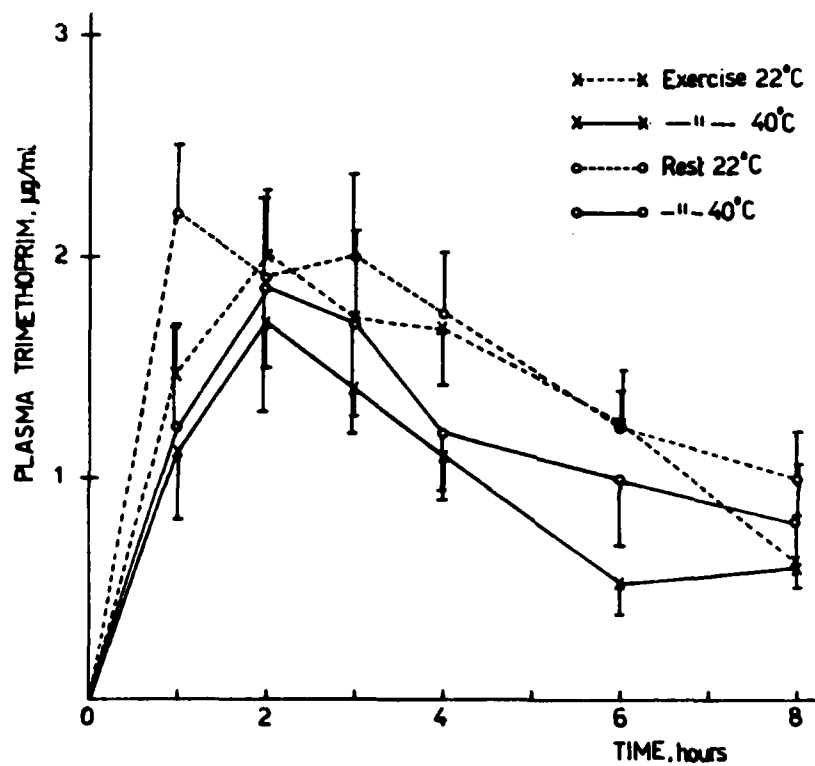


Figure 8: Mean (\pm SEM) plasma trimethoprim in 6 subjects under experimental conditions as indicated.

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